# Neuropsychological Performance in Pediatric Bipolar Disorder

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***Background:*** *Growing awareness of childhood bipolar disorder necessitates further cognitive neuroscience research to determine unique developmental differences between pediatric and adult onset bipolar disorder. We sought to examine whether neuropsychological function in children with bipolar disorder resembles that in adults with the illness and to extend our knowledge about cognitive function in pediatric bipolar disorder.*

***Methods:*** *We administered a computerized neuropsychological test battery known as the Cambridge Neuropsychological Test Automated Battery to a sample of 21 children and adolescents with bipolar disorder and compared them with 21 age- and gender-matched controls.*

***Results:*** *In comparison to controls, children with bipolar disorder were impaired on measures of attentional set-shifting and visuospatial memory. Post hoc analyses in pediatric bipolar disorder subjects did not show significant associations between neuropsychological performance and manic symptomatology or attention-deficit/hyperactivity disorder comorbidity.*

***Conclusions:*** *Cambridge Neuropsychological Test Automated Battery data presented here in pediatric bipolar disorder fit well within the broader framework of known neurocognitive deficits in adult bipolar disorder. Our pediatric bipolar disorder subjects demonstrated selective deficiencies in attentional set-shifting and visuospatial memory. Our work suggests altered ventrolateral prefrontal cortex function, especially when linked to other lesion and neuroimaging studies.* Biol Psychiatry 2004;55:32–39 © *2004 Society of Biological Psychiatry*

**Key Words:** Bipolar disorder, child, psychological tests, neuropsychology

The study of pediatric bipolar disorder (BD) is currently one of the most active and controversial areas of child psychiatry research (Geller et al 2002b, 2002c; Wozniak and Biederman 1997). Considerable work has focused on the diagnosis of pediatric BD, as well as the challenge of differentiating it from attention-deficit/hyperactivity disorder (ADHD) (Carlson 1998; Biederman et al 1998); however, few have examined the pathophysiology of pediatric BD. The use of neuropsychological test paradigms developed from the perspective of cognitive neuroscience has the potential to advance our understanding of the neural mechanisms mediating the symptoms of BD in both children and adults (Leibenluft et al 2003a).

Studies indicate that adults with BD have neuropsychological deficits in attention and declarative memory. During manic or mixed episodes, adults with BD demonstrate inattention on the continuous performance task (Sax et al 1995) and on trail making A and B (Basso et al 2002). Similar findings have been replicated in euthymic adults with BD (Wilder-Willis et al 2001; Neu et al 2001; Ferrier et al 1999). With respect to memory, euthymic adults with BD show deficits in declarative memory on the California Verbal Learning Test, Controlled Oral Word Association Test (FAS Verbal Fluency), and Digit Span (Cavanagh et al 2002; van Gorp et al 1999; Ferrier et al 1999). In addition, declarative memory deficits have been demonstrated in BD-depressed episode adults on the Rey Auditory Verbal Learning Test and the Controlled Oral Word Association Test (FAS Verbal Fluency) (Wolfe et al 1987). In short, studies of adults with BD consistently show deficits in attention and declarative memory persisting across mood states, possibly indicating trait neuropsychological impairment in patients with BD.

We sought to fill a critical need by extending our knowledge about cognitive function in pediatric BD. To that end, we administered the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Cambridge Cognition Ltd., Cambridge, United Kingdom) to a sample of children and adolescents with BD. The CANTAB is a computerized battery comprised of subtests probing different aspects of cognition, including attention and memory (Sahakian and Owen 1992). Subjects respond to visually presented stimuli by pressing a touch-sensitive screen. Several investigators have examined CANTAB data in adult subjects with BD (Table 1). Consistent with data obtained on other measures, manic adults demonstrate deficits in sustained, focused attention and working memory on the CANTAB (Clark et al 2001; Murphy et al 1999). Adults in a mixed or manic state demonstrate deficits in working and episodic memory, spatial attention, and problem-solving in comparison both with BD-depressed episode adults and to controls (Sweeney et al 2000). In the same study, depressed adults with BD were found to have only impaired episodic memory in comparison with mixed/manic BD subjects and controls. Euthymic BD adults demonstrate deficits in attentional set-shifting and visuospatial working memory in comparison with controls (Clark et al 2002; Rubinsztein et al 2000). Thus, CANTAB data in adults with BD may indicate trait impairments of attention and working memory.

In this article, we present pilot neuropsychological data from seven CANTAB subtests in a sample of children meeting *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) criteria for BD (American Psychiatric Association 1994). These children are all participants in a naturalistic study of childhood-onset BD ongoing at the National Institute of Mental Health (NIMH). Based on the adult BD literature, we expected to find deficits among pediatric BD subjects in comparison with age- and gender-matched controls on those subtests assessing attention and memory. The CANTAB measures were adminis-

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**Table 1.** Cambridge Neuropsychological Test Automated Battery (CANTAB) Subtest Findings in Adults with Bipolar Disorder

| Author | Study Group(s) | BD Significantly Impaired versus Comparison Group | BD Not Significantly Different from Controls |
|---|---|---|---|
| Murphy et al (1999) | Manic BD vs. NC[a] | DMTS, PRM, SRM, TOL | SMTS |
| Sweeney et al (2000) | Manic/Mixed BD vs. Depressed BD vs. NC | PAL, SOC, SRM, SSP, SWM, DMTS, SMTS | ID/ED |
| Clark et al (2001) | Manic BD Adults vs. NC | ID/ED, PRM, RVIP, SRM, SWM, TOL | —— |
| Rubinsztein et al (2000) | Euthymic BD vs. NC | DMTS, PRM, SRM | ID/ED, SMTS, TOL |
| Clark et al (2002) | Euthymic BD vs. NC | ID/ED, RVIP | SWM, TOL |

BD, bipolar disorder, NC, normal control, CANTAB, Cambridge Neuropschological Test Automated Battery; PAL, Paired Associate Learning; ID/ED, Intradimensional/Extradimensional Shift; PRM, Pattern Recognition Memory; SRM, Spatial Recognition Memory; SWM, Spatial Working Memory; DMTS, Delayed Match To Sample; SMTS, Simultaneous Match To Sample; TOL/SOC, Tower of London/Stockings of Cambridge; SSP, Spatial Span; PAL, Paired Associate Learning; RVIP, Rapid Visual Information Processing.

[a]A third study group with Major Depressive Disorder was later used to compare reaction times, but no CANTAB subtest data were presented.

tered as part of a larger series of neuropsychological and psychophysiological tests aimed at understanding the phenomenology and pathophysiology of pediatric BD.

## Methods and Materials

### Subjects

Subjects ($n = 21$) were enrolled in a naturalistic study of BD in children aged 6 to 17 years at the National Institute of Mental Health. The NIMH Institutional Review Board approved the study. Parents gave informed consent and children gave their assent before participation. Pediatric BD subjects were recruited through advertisements placed on web sites of relevant support groups and distributed at professional conferences, and a letter about the study was sent to child psychiatrists nationally. Inclusion criteria consisted of meeting DSM-IV criteria for BD; involvement with ongoing mental health treatment; and presence of at least one primary caretaker who could grant informed consent and participate in the research process. Regarding DSM-IV BD criteria, all subjects had a history of at least one episode during which the child exhibited elation and/or grandiosity and a total of at least three DSM-IV criterion B mania symptoms (Geller et al 2002c). Children with a history of irritability only, without elation or grandiosity, were excluded. Of the 21 pediatric subjects in the BD sample, 18 met full duration criteria ($> 4$ days of hypomania or mania) and 3 met criteria for BD-Not Otherwise Specified with the longest episode 1 to 3 days. Exclusion criteria were as follows: intelligence quotient (IQ) $< 70$; autistic disorder or severe pervasive developmental disorder; psychosis that interferes with the child's capacity to understand and comply with study procedures; unstable medical illness (i.e., severe asthma); medical illness that could cause the symptoms of bipolar illness (i.e., multiple sclerosis, thyroid disease); pregnancy; or substance abuse within 2 months of the initial evaluation. Following a telephone screening, those patients who were thought likely to meet inclusion criteria were invited to NIMH with a primary caregiver for a more detailed screening. This included the Kiddie-Schedule for Affective Disorders Present and Lifetime Version (K-SADS-PL) with parent and child individually screened (Kaufman et al 1997). Trained clinicians with graduate level training and established interrater reliability completed the K-SADS-PL, as well as mood ratings, which included Young Mania Rating Scale (YMRS), Children's Depression Rating Scale (CDRS), Children's Depression Inventory (CDI), and Global Assessment of Functioning (GAF). All diagnoses were applied based on best estimate procedures (Leckman et al 1982), generated in a consensus conference of research staff led by two psychiatrists. All subjects were asked to remain on a stable medication regimen for 14 days before baseline testing.

Controls ($n = 21$) were matched with patients for age and gender. Control inclusion criteria consisted of negative psychiatric history in control subject and her/his first-degree relatives, normal physical and neurologic examinations, not currently taking any form of medication, and an identified primary care physician. Exclusion criteria for controls included IQ $<70$; ongoing medical illness; neurologic disorder (including seizures); pregnancy; past or present substance abuse; and history of sexual abuse.

Following screening, acceptance into study, and informed consent, study participants completed the selected CANTAB subtests.

### Description of CANTAB Subtests

**Motor Screening.** The motor screening test (MOT) is a simple pointing task. Crosses are shown one at a time in different locations on the touch-sensitive screen. Subjects must touch the cross once it begins to flash colors. The primary outcome variable is response latency in milliseconds.

**Pattern Recognition Memory.** In pattern recognition memory (PRM), subjects view a series of 12 shapes, one at a time. Then, pairs of shapes are presented, one novel and one from the previously presented series. Subjects must select the familiar shape, rather than a novel one, within the pair. Data collected include mean latency to correct responses, as well as both number and percent correct.

**Spatial Memory Span.** The spatial memory span (SSP) test of working memory is modeled after the Corsi Block Test. Subjects watch squares on the screen change colors, one at a time, from white to a different color. The sequence varies across trials. Subjects then must touch the squares on the screen in the same sequence in which they changed colors. The number of blocks increases from 2 to 9 across trials. Length of memory span is measured, in addition to total errors and total usage errors. Total errors are defined as number of times the subject selected an incorrect box. Total usage errors are the number of times the subject selected a box not in the sequence being recalled.

**Spatial Recognition Memory.** In spatial recognition memory (SRM), subjects watch a series of squares appear and disappear at various locations on the touch screen. Then, they are presented with a pair of squares, one of which is in a location previously

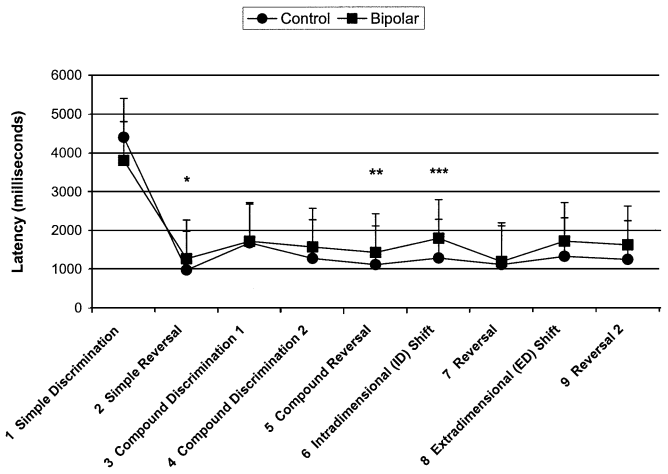


**Figure 1.** Intra/extradimensional shift latency by stage.
*$t=2.14$, $df=19.77$, $p=.05$; **$t=-2.97$, $df=20.41$, $p=.04$; ***$t=-2.97$, $df=18.88$, $p=.008$.

presented and one of which is not. Subjects must choose the one square presented in the previously presented location. Data collected include mean latency to correct response and both number and percent correct.

**Spatial Working Memory.** In spatial working memory (SWM), subjects must touch boxes displayed on the screen to "open" them to reveal the blue token "hidden" within one of them. Subjects then use their finger to move the blue token into an empty column on the right side of the screen. The task becomes increasingly difficult as the total number of boxes presented in a trial increases to four, six, and eight. Subjects must remember not to return to a box in which they have previously found a token (between search error) and not to search the same box twice in the same trial (within search error). In addition to recording errors, a strategy score is collected, with a lower strategy score corresponding to fewer returns to previously selected boxes.

**Stockings of Cambridge.** In the Stockings of Cambridge (SOC), a modified version of the Tower of London task, subjects move three colored balls from one location to another to mimic a model provided by the computer. The task becomes progressively more difficult as the minimum number of moves required to complete the task increases from two to three, four, and ultimately five moves. Data collected include number of moves, problems solved in minimum moves, mean initial thinking time, and subsequent thinking time across all levels (two, three, four, and five minimum moves) and mean subsequent thinking time.

**Intradimensional/Extradimensional Shift.** The intradimensional/extradimensional (ID/ED) shift, a set-shifting task, mirrors the Wisconsin Card Sorting Task (WCST). The task has nine stages requiring the subject to successfully complete six trials in each to proceed to the next stage. If subjects do not successfully complete six trials in a total maximum of 50 attempts, the test is discontinued. First, subjects choose one of two purple shapes (i.e., square or circle) presented without an explicit instruction about which is correct. Stimuli are always presented as pairs. Subjects learn from trial and error what initial construct (i.e., preference for purple squares rather than purple circles) is being reinforced. Stimuli are initially purple shapes, but then white line designs are added as distracters during stage 3. Throughout stages 1 through 7, reinforcement continues to depend on the shape that is chosen, with line design being irrelevant. Stage 6 is known as the intradimensional shift because, while all of the stimuli are changed (i.e., both lines and shapes), choice of the correct shape continues to determine reinforcement. Stage 8 is the extradimensional shift because it is the first stage at which the previously irrelevant construct (i.e., choice of the correct white line design) is rewarded. Stages 2, 5, 7, and 9 are reversal stages requiring subjects to continue to respond to the same construct as in the previous stage (either shape or line) but to reverse the exemplar chosen. For example, if during stage 1 purple squares are rewarded rather than purple circles, then during stage 2 purple circles will be rewarded rather than purple squares (the opposite of stage 1). Data collected include errors, latency, and number of trials to reach criteria successfully in each stage individually, in all trials before the ED shift (i.e., stages 1 through 7 "pre-Extradimensional shift"), and at and after the ED shift (i.e., stages 8 and 9 "Extradimensional shift").

### Statistical Analysis

The data were analyzed using Statistical Package for Social Sciences (SPSS, Inc., Chicago, Illinois) version 11.5. We conducted $t$ tests for continuous variables adjusted for unequal variances via Levene's test. Significance was set at $\leq .05$. We attempted to balance the potential for type I and type II errors in this study, the first to use the CANTAB in pediatric BD. As a result, we present all significant results, without correction for multiple comparisons; however, in interpreting our results, we emphasize results that either meet a more stringent level of statistical significance ($p < .01$) or that confirm results previously documented in adults with BD.

After examining between-group differences, we used a set of secondary analyses to examine the relationship between symptom levels and neuropsychological performance. Specifically, post hoc Spearman correlations were examined between Young Mania Rating Scale and those CANTAB subtests that showed significant differences between patients and controls. To consider the effect of ADHD on CANTAB results, BD children with current ADHD were compared to BD subjects without current ADHD using an unpaired independent samples $t$ test.

## Results

The sample consisted of 21 children with pediatric BD and 21 normal controls (NC), each with 15 boys and 6 girls (Table 2). Mean age was 12.74 ± 2.37 in the BD group and 12.68 ± 2.36 in the NC group. Pediatric BD subjects and normal controls did not differ in full-scale IQ (FSIQ) (pediatric BD FSIQ mean 109.3 ± 15.5; NC mean 114.7 ± 10.5). The sample was euthymic with a Young Mania Rating Scale-Parent (YMRS-P) mean of 9.19 ± 8.14 and Young Mania Rating Scale-Child (YMRS-C) mean of 3.71 ± 4.51 (Young et al 1978; Fristad et al 1992). Children's Depression Rating Scale-Parent (CDRS-P) mean was 27.19 ± 9.42, and Children's Depression Rating Scale-Child (CDRS-C) mean was 23.67 ± 7.85. Children's Depression Inventory mean was 9 ± 8.47. The BD sample was moderately impaired, with a mean GAF score during the week before testing of 59.1 ± 8.60.

Further analysis of our sample's mood ratings revealed heterogeneity. Young Mania Rating Scale ratings less than 12 indicate euthymia, between 12 and 25 indicate hypomania, and greater than 25 indicate mania (Youngstrom, personal communication, March 2002). Children's Depression Rating Scale scores $> 40$ indicate moderate depression requiring treatment in clinical trials (Emslie et al 2002). Our current sample of 21 BD children consisted of 13 children with YMRS $\leq 12$ and 8 children with YMRS 12 to 25. None were manic with YMRS $> 25$. Of those with YMRS $\leq 12$, 11 had CDRS $< 40$ and would be categorized as euthymic. Of those with YMRS 12 to 25, 7 had CDRS $< 40$ and 1

**Table 2.** Sample Characteristics

| | Bipolar Subjects ($n = 21$) | Normal Controls ($n = 21$) |
|---|---|---|
| Gender | 15 male; 6 female | 15 male; 6 female |
| Age | 12.74 ± 2.37 | 12.68 ± 2.36 |
| Full-Scale IQ | 109.3 ± 15.5 | 114.7 ± 10.5 |
| YMRS[a] | | |
| YMRS-parent | 9.19 ± 8.14 | – |
| YMRS-child | 3.71 ± 4.51 | – |
| CDRS[b] | | |
| CDRS-parent | 27.19 ± 9.42 | – |
| CDRS-child | 23.67 ± 7.85 | – |
| CDI[c] | 9 ± 8.47 | – |
| GAF-Past Week[d] | 59.10 ± 8.60 | – |

Full-scale IQ data were not obtained in 3/21 pediatric BD subjects and 2/21 normal controls. Mood data were not obtained for controls as they did not, by definition, meet diagnostic criteria for any psychiatric disorder.

IQ, intelligence quotient; YMRS, Young Mania Rating Scale; CDRS, Child Depression Rating Scale; CDI, Children's Depression Inventory; GAF, Global Assessment of Functioning.

[a]YMRS < 12 indicates euthymia, 12–25 hypomania, >25 mania.

[b]CDRS > 40 indicates moderate depression.

[c]*T*-scores calculated by age and gender. In our current sample, CDI *t*-scores average 48.3 ± 11.9. *T*-scores > 70 are considered abnormally elevated and possibly indicate depression.

[d]GAF < 50 indicates serious symptoms or impairment.

**Table 3.** Medications of Patients with Childhood-Onset Bipolar Disorder at the Time of Testing

| Medications by Class | Number of Subjects | Percent of Subjects |
|---|---|---|
| Lithium (Lithobid ®, Eskalith ®) | 12 | 54.5 |
| Antiepileptic Drugs (AEDs) | | |
| Valproate (Depakote ®) | 10 | 45.4 |
| Topiramate (Topomax ®) | 3 | 13.6 |
| Oxcarbazepine (Trileptal ®) | 2 | 9.1 |
| Carbamazepine (Tegretol ®) | 1 | 4.5 |
| Gabapentin (Neurontin ®) | 1 | 4.5 |
| Lamotragine (Lamictal ®) | 1 | 4.5 |
| Atypical Neuroleptics | | |
| Risperidone (Risperdal ®) | 8 | 36.4 |
| Quetiapine (Seroquel ®) | 4 | 18.2 |
| Ziprasidone (Geodon ®) | 2 | 9.1 |
| Clozapine (Clozaril ®) | 1 | 4.5 |
| Olanzapine (Zyprexa ®) | 1 | 4.5 |
| Selective Serotonin Reuptake Inhibitors (SSRI) | 3 | 13.6 |
| Fluvoxamine (Luvox ®) | | |
| Paroxetine (Paxil ®) | | |
| Citalopram (Celexa ®) | | |
| Psychostimulants | | |
| Methylphenidate (Ritalin, Metadate ®, Focalin ®) | 5 | 22.7 |
| Dextroamphetamine (Dexedrine®, Adderall®) | 2 | 9.1 |
| Other | | |
| Alpha-adrenoceptor agonist (clonidine, guanfacine) | 3 | 13.6 |
| Benzodiazepine (clonazepam, lorazepam) | 3 | 13.6 |
| Thyroid supplementation | 3 | 13.6 |
| Buproprion (Wellbutrin ®) | 2 | 9.1 |
| Venlafaxine (Effexor ®) | 2 | 9.1 |
| Buspirone (BuSpar ®) | 1 | 4.5 |

had a CDRS of 43. Thus, our current pediatric BD sample included those who were euthymic and who had hypomania without depression.

All BD subjects were taking at least one psychotropic medication at the time of testing ($n = 1$ (4.5%) was taking one medication; $n = 4$ (18.2%) were taking two medications; $n = 6$ (27.3%) were taking three medications; and $n = 11$ (52.3%) were taking four or more medications). Table 3 indicates the patients' medications at the time of testing. In the bipolar group, 57% met criteria for comorbid current ADHD and 71% met ADHD criteria during their lifetime.

Group comparisons of CANTAB results between patients and controls yielded significant differences on the following subtests: pattern recognition memory, spatial span, and intradimensional/extradimensional shift (Table 4). Bipolar disorder subjects' performance was not significantly different from that of controls on the remainder of the CANTAB tests, including Motor Screening, Spatial Working Memory, Stockings of Cambridge, and Spatial Recognition Memory.

On the ID/ED shift, BD subjects made significantly more pre-extradimensional shift errors than controls (BD mean = 14.13 ± 9.97; NC mean = 6.63 ± 3.74; $t = 2.83$; $df = 19.1$; $p = .01$). They also required more total trials to complete all attempted stages (BD mean = 101.75 ± 26.94; NC mean = 83.69 ± 13.22; $t = 2.41$; $df = 30$; $p = .02$). No significant differences between BD subjects and normal controls were found on any other ID/ED subtest. Further examination of ID/ED results by stage (Figures 1 and 2) indicates BD subjects are impaired during the simple reversal stage with more trials to successfully complete the stage (BD mean = 11.53 ± 5.93; NC mean 7.87 ± 1.96; $t = -2.28$; $df = 17.02$; $p = .04$), more errors (BD mean = 2.67 ± 2.13; NC mean = 1.20 ± .41; $t = -2.62$; $df = 15.06$; $p = .02$), and longer latency (BD mean = 1268.93 ± 480.89; NC mean = 975.47 ± 223.22; $t = -2.14$; $df = 19.77$; $p = .05$).

With respect to PRM, BD subjects had significantly longer mean latencies on correct responses (BD mean = 2500.72 ± 723.08; NC mean = 1979.89 ± 596.45; $t = 2.82$, $df = 30$, $p = .01$). When effects of simple motor latency (motor screening latency) were controlled for via a post hoc univariate analysis of covariance, children with BD and controls differed significantly on PRM mean correct latency [$F(1,33) = 4.96$, $p = .03$]. Thus, BD subjects' longer PRM latencies are not the result of more generalized motor slowing. Percent correct (BD mean = 88.24 ± 12.26; NC mean = 94.36 ± 4.64; $t = -1.93$, $df = 20.5$; $p = .07$) was not significantly different between BD subjects and controls.

On SSP, BD subjects had significantly reduced span length (BD mean = 5.82 ± 1.12; NC mean = 6.82 ± 1.33; $t = -2.36$, $df = 32$, $p = .03$); however, there were no significant differences between BD subjects and controls on total errors (the number of times the subject selected an incorrect box; BD mean = 15.06 ± 4.84; NC mean = 15.88 ± 7.68; $t = -.37$; $df = 31$; $p = .72$) or total usage errors (the number of times a subject selected a box not in the original sequence; BD mean = 3.41 ± 2.18; NC mean = 2.18 ± 1.62; $t = 1.97$; $df = 32$; $p = .06$).

Post hoc analyses examined associations between neuropsychological performance and manic symptomatology or ADHD comorbidity in patients with BD. There were no significant associations between mania symptomatology and neuropsychological performance on ID/ED, PRM, or SSP ($p > .05$ for all analyses). With respect to ADHD comorbidity, independent samples *t* test failed to show any significant differences between BD children with current ADHD and BD children without current ADHD.

**Table 4.** Cambridge Neuropsychological Test Automated Battery (CANTAB) Results

| CANTAB Parameter | *n* (BD) | *n* (NC) | Bipolar Subjects | Normal Controls | *t* | *df* | *p* |
|---|---|---|---|---|---|---|---|
| Motor Screening (MOT) Mean latency (ms) | 18 | 18 | 1092.03 ± 514.38 | 1268.09 ± 806.20 | .78 | 34 | .44 |
| Intra/Extradimensional Shift (ID/ED) | | | | | | | |
| Completed stage errors | 16 | 16 | 17.25 ± 8.71 | 13.38 ± 6.32 | 1.44 | 30 | .16 |
| Completed stage trials | 16 | 16 | 83.00 ± 22.82 | 74.31 ± 16.58 | 1.23 | 30 | .23 |
| Number of errors made prior to extradimensional shift | 16 | 16 | 14.13 ± 9.97 | 6.63 ± 3.74 | 2.82 | 19.1 | .01[a] |
| Extradimensional stage errors | 16 | 16 | 9.31 ± 9.79 | 10.38 ± 9.29 | .32 | 30 | .76 |
| Total errors | 16 | 16 | 26.25 ± 13.99 | 18.38 ± 8.15 | 1.95 | 24.1 | .06 |
| Stages completed | 16 | 16 | 8.06 ± 1.61 | 8.63 ± .81 | 1.25 | 30 | .22 |
| Total trials | 16 | 16 | 101.75 ± 26.94 | 83.69 ± 13.22 | 2.41 | 30 | .02[a] |
| Pattern Recognition Memory (PRM) | | | | | | | |
| Mean correct latency (ms) | 17 | 17 | 2500.72 ± 723.08 | 1979.90 ± 596.45 | 2.29 | 32 | .01[a] |
| Percent correct | 17 | 17 | 88.24 ± 12.26 | 94.36 ± 4.64 | 1.93 | 20.5 | .07 |
| Spatial Span (SSP) | | | | | | | |
| Total errors | 17 | 16 | 15.06 ± 4.84 | 15.88 ± 7.68 | .37 | 31 | .72 |
| Span length | 17 | 17 | 5.82 ± 1.13 | 6.82 ± 1.33 | 2.36 | 32 | .03[a] |
| Total usage errors | 17 | 17 | 3.42 ± 2.18 | 2.12 ± 1.62 | 1.97 | 32 | .06 |
| Spatial Recogntion Memory | | | | | | | |
| Mean correct latency (ms) | 17 | 17 | 3091.76 ± 1246.51 | 3047.36 ± 2463.91 | .07 | 32 | .95 |
| Percent correct | 17 | 17 | 67.65 ± 13.71 | 76.18 ± 12.31 | −1.909 | 32 | .07 |
| Spatial Working Memory (SWM) | | | | | | | |
| Strategy (low score = effective use) | 18 | 18 | 33.06 ± 7.96 | 31.83 ± 3.97 | .58 | 34 | .56 |
| Total errors | 18 | 18 | 32.89 ± 18.70 | 26.50 ± 19.16 | 1.01 | 34 | .32 |
| Stockings of Cambridge (SOC) | | | | | | | |
| Mean moves (2 moves) | 17 | 17 | 2.00 ± .00 | 2.00 ± .00 | | | |
| Mean moves (3 moves) | 17 | 17 | 3.42 ± .62 | 3.47 ± .51 | .30 | 32 | .77 |
| Mean moves (4 moves) | 17 | 17 | 4.71 ± 1.16 | 5.35 ± .93 | 1.79 | 32 | .08 |
| Mean moves (5 moves) | 17 | 17 | 7.88 ± 2.00 | 6.82 ± 1.42 | 1.78 | 32 | .09 |
| Problems solved in minimum moves | 17 | 17 | 7.59 ± 1.97 | 7.82 ± 1.78 | .37 | 32 | .72 |

CANTAB, Cambridge Neuropsychological Test Automated Battery; BD, pediatric bipolar disorder subject; NC, normal control.
[a]$p = < .05$

## Discussion

Despite the considerable literature on the clinical presentation of pediatric BD, few studies have evaluated neuropsychological function in these patients. Here, we found significant differences between children with BD and age- and gender-matched controls on measures from the following CANTAB subtests: intradimensional/extradimensional shift, pattern recognition memory, and spatial span; however, there were no differences between patients and controls on motor screening, spatial recognition memory, spatial working memory, and Stockings of Cambridge. Given our small sample size and the fact that the children were taking medication during testing, these data should be considered preliminary.

On the ID/ED shift, children with BD had significantly more pre-extradimensional shift errors and significantly more trials overall. Consistent with the findings in our sample, Sweeney et al (2000) found increased pre-extradimensional shift errors in adult BD subjects, regardless of mood state, compared to controls or to patients with unipolar depression, though this failed to reach significance. Clark et al (2001) found manic adults had greater number of reversal errors, summed across all stages of the ID/ED task, as well as a greater number of ED shift errors. In another study, Clark et al (2002) found euthymic adults with BD made significantly more total errors on ID/ED shift in comparison to normal controls. Thus, our results suggest continuity between pediatric and adult BD with respect to impaired attentional set-shifting.

Examination of our ID/ED results by stage reveals significant deficits across all parameters (i.e., errors, latency, and trials to successfully complete the stage) during the first reversal stage. This finding aligns with the Clark et al (2001) finding of increased reversal errors among manic adult subjects. It is interesting to note that, while our subjects with BD were impaired on the simple reversal stage, they persisted and completed the remainder of the ID/ED stages. Despite the fact that children with BD are generally reported to be irritable, our subjects did not become irritable, frustrated, and/or refuse to complete the full task (Leibenluft et al 2003b; Geller et al 2002b). While adults with unipolar depression may demonstrate increased sensitivity to negative feedback on the CANTAB, our present study was not designed to detect such an effect (Elliott et al 1996, 1997); however, additional work is needed to determine whether children with BD demonstrate performance decrements in response to negative feedback or increased task complexity.

A growing body of research has begun to identify functional neuroanatomical regions responsible for alterations in attentional set-shifting. In nonhuman primate lesion studies using the ID/ED shift, monkeys demonstrate a double dissociation of inhibitory control within the prefrontal cortex (PFC). Lateral PFC lesions

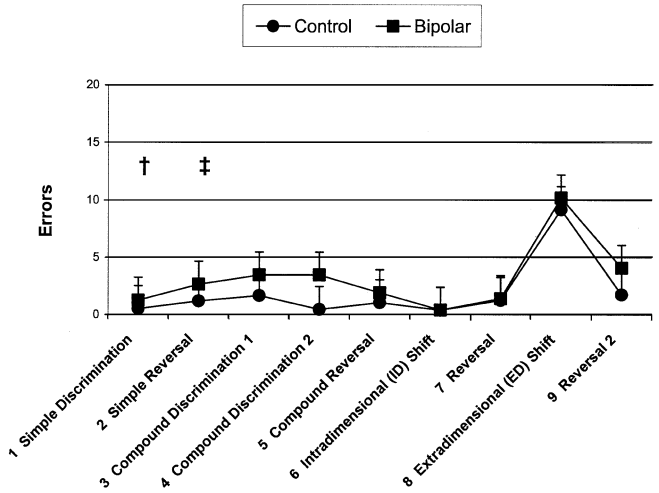


**Figure 2.** Intra/extradimensional shift errors by stage.
†$t=-2.08$, $df=21.18$, $p=.05$; ‡$t=-2.82$, $df=16.08$, $p=.02$.

selectively impair attentional set-shifting between perceptual dimensions, such as ED shift. Orbital PFC lesions selectively impair the ability to reverse stimulus-reward associations within a specific perceptual dimension, such as reversal stages of ID/ED task (Dias et al 1996, 1997). Moreover, functional magnetic resonance imaging (fMRI) studies of normal adult humans indicate ventrolateral PFC and ventral striatum involvement in reversal learning (Cools et al 2002). Our BD subjects were especially impaired on the first simple reversal stage, with increased number of errors and trials required to complete the stage. Also, whereas BD subjects had shorter latency than controls during the first simple discrimination stage, BD subjects had significantly longer latency than controls on the simple reversal stage. Our BD sample was not impaired across all three stage parameters simultaneously (trials, errors, and latency) on any other reversal stage, though they did have significantly longer latency on the compound reversal stage. Thus, there is a need to further investigate potentially altered reversal learning in BD, suggestive of altered frontostriatal activity.

On the PRM subtest, BD subjects demonstrated significantly longer response latencies that were not representative of generalized motor slowing. Several studies of adults with BD have reported PRM deficits. For example, Murphy et al (1999) found that manic adults demonstrated impaired proportion correct and had longer response latencies than did controls. Sweeney et al (2000) compared two groups of adults with BD (one in a manic or mixed state and another in a depressed state), a group with major depressive disorder, and a control group. All three patient groups had deficits in percent correct on the PRM subtest compared to controls. Rubinsztein et al (2000) examined euthymic bipolar adults and found significant deficits in proportion correct but no significant difference in PRM response latency. To our knowledge, no study of BD patients has reported completely unimpaired performance on PRM; however, these deficits may represent a more generalized deficit characteristic of mood disorders, not just BD, as similar deficits have been found in unipolar depressed patients (Beats et al 1996). Nevertheless, the presence of prolonged latency in the absence of a difference in percent correct suggests pediatric BD is associated with subtle impairments on the PRM.

Children with BD in our study also demonstrated significantly decreased span length on the SSP subtest. Adults with BD show deficits in span length in comparison to controls while manic, mixed, or depressed; similar deficits are also seen in those with unipolar depression (Sweeney et al 2000; Kempton et al 1999). Thus, like deficits in PRM, deficits in SSP may not be specific to any specific mood disorder or to ADHD.

Our finding of deficits on PRM and SSP but no deficits on SOC, SRM, or SWM in pediatric BD subjects is consistent with studies demonstrating a division of working memory for objects versus working memory for location. Owen et al (1995, 1996) found a double dissociation of PFC function using the CANTAB and other, related paradigms in patients following neurosurgical resection of amygdalo-hippocampal, frontal, or temporal cortices and in a positron emission tomography (PET) study of controls. Recognition of object features, as required on the PRM, was associated with activation of the ventral prestriate and inferior temporal cortices. In contrast, recognition of object location, as required on the SRM, was associated with activation of the dorsal prestriate and posterior parietal cortex. These findings are consistent with a number of fMRI and PET studies demonstrating that storage of information regarding object identity is primarily localized to the ventrolateral PFC (ventral stream) while working memory for object location is focused in the dorsolateral prefrontal cortex (dorsal stream) (D'Esposito et al 1998; D'Esposito and Postle 1999; Ungerleider et al 1998). Thus, our finding of PRM and SSP deficits but unimpaired SOC, SRM, and SWM may implicate ventrolateral PFC dysfunction in the pathophysiology of pediatric BD. Moreover, our PRM and SSP findings mesh well with our ID/ED findings, also implicating ventrolateral PFC dysfunction in pediatric BD; however, neuroimaging work is needed in pediatric BD to define possible developmental differences in PFC activity, since studies of manic adult BD subjects have found significant decreases in both PET activation and MRI volume in the orbitofrontal cortex (Blumberg et al 1999; Rubinsztein et al 2001; Sax et al 1999; Starkstein and Robinson 1997).

Issues of comorbid ADHD, concomitant medication, and mood state, each of which may affect neuropsychological performance, complicate the interpretation of our data. Many authors have reported high comorbidity between childhood-onset BD and ADHD (Faraone et al 1997; Biederman et al 2000). In general, while studies address neuropsychological function in childhood ADHD and adult BD, there are few neuropsychological studies of children or adolescents with BD (Lagace et al 2003). Research on children with BD could provide a framework for identifying commonalities and distinctions between pediatric BD and ADHD. One study using the CANTAB in children with ADHD found that stimulant naïve ADHD children, in comparison to both stimulant-treated ADHD children and controls, perform poorly across subtests of attention and memory, including spatial span, spatial working memory, Tower of London, ID/ED shift, spatial recognition memory, and delayed matching to sample (Kempton et al 1999). In fact, the only subtest Kempton et al (1999) administered that did not demonstrate impaired performance by stimulant naïve ADHD subjects was pattern recognition memory, which was impaired in our current pediatric BD sample. In our present study, pediatric BD subjects with current ADHD diagnosis did not perform significantly differently from subjects without current ADHD, although the power of our analysis is limited. Our pediatric BD sample seemed to perform more similarly to adults with BD in the type of deficits demonstrated and less like children with ADHD, who had more generalized CANTAB deficits; however, further study of pediatric BD subjects while medicated and unmedicated, as well as with

and without comorbid ADHD, is required to identify differences in the neuropsychological profiles of pediatric BD and ADHD.

The relationship between medication and neuropsychological performance is complex. All of our subjects with BPD were taking at least one psychotropic medication at time of testing, and 50% were taking four or more medications. Given the design of this study, it was not possible to study the BPD children while medication free. Nevertheless, our study population is representative of other studies reporting neuropsychological findings in adult BPD patients, both in terms of the percentage of the sample currently taking psychotropic medication and in terms of the classes of medication that the patients were receiving. Moreover, our results are clinically meaningful since our sample's medication status is representative of children with BPD in the community. Further study in a larger sample would be necessary to determine the effect of medication number and type on neuropsychological performance.

Like medication, the effect of bipolar subjects' mood state on neurocognitive function is complex. In our current sample, no significant correlations existed between YMRS-P rating and PRM, SSP, and ID/ED CANTAB subtests. Current studies of adult BD have found neurocognitive deficits in memory and declarative memory during depression, euthymia, and mania. This suggests that neurocognitive abnormalities may be a trait feature of BD itself, rather than being secondary to mood state (Zubieta et al 2001; Basso et al 2002; Neu et al 2001; Sax et al 1999). Also, a number of studies indicate that trait neuropsychological impairments in attention and declarative memory may be worse with increasing severity of BD, as indicated by number of hospitalizations or number of manic and depressive episodes (Denicoff et al 1999; Bearden et al 2001; Tham et al 1997). Further work is needed in pediatric BD to determine if neurocognitive performance reflects mood-state changes or trait neuropsychological impairment.

In conclusion, our current preliminary work begins to fill the void of neuropsychological investigations into the unique developmental aspects of pediatric BD. Cambridge Neuropsychological Test Automated Battery data presented here on pediatric BD fit well within the broader framework of known neurocognitive deficits in adults with BD. Our pediatric BD subjects demonstrate selective deficiencies in attentional set-shifting and visuospatial memory. Our work suggests altered ventrolateral PFC function, especially when linked to other lesion and neuroimaging studies. Growing awareness of childhood BD necessitates further cognitive neuroscience research to determine unique developmental differences between pediatric and adult onset BD, as well as between BD and ADHD.

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